Smoking in spondyloarthritis: unravelling the complexities

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Abstract

Tobacco smoking is a major threat to health. There is no doubt about the need to promote and support cessation at every opportunity. Smoking has a clear role in rheumatoid arthritis, but what evidence is there that the same relationship exists in spondyloarthritis? In this review, we examine (the less cited) paradoxes and contradictions in existing axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) literature; for example, smoking appears to be 'protective' for some axSpA manifestations. We also highlight findings from higher quality evidence: smoking is associated with increased risk of PsA and the risk of psoriasis in axSpA. The relationship between smoking and SpA is far from simple. Our aim is to highlight the harms of smoking in SpA and bring attention to inconsistencies in the literature to inform further research.

Keywords: axial spondyloarthritis, ankylosing spondylitis, psoriatic arthritis, extra-articular manifestations, uveitis, psoriasis, arthritis, smoking, tobacco, observational studies.

Key messages:

1) Smoking cessation should be supported at every opportunity given the harms to general health.
2) There are many inconsistencies in the literature regarding the impact of smoking on spondyloarthritis.
3) Paradoxical associations suggesting a 'protective' effect of smoking may be explained by collider bias.

Introduction

Tobacco smoking is one of the greatest threats to health in our time. The World Health Organization estimates that there are 7 million deaths per year as a direct result of tobacco use and a further 1.2 million through second-hand smoke [1]. In the UK, approximately 17% of all deaths in the past 10 years have been attributed to smoking [2]. Its direct causal contribution to morbidity is also clear, such as cardiorespiratory and malignant diseases. The message to all healthcare professionals is therefore clear: support smokers to quit at every opportunity. In rheumatology, there is consistent evidence that smoking has a detrimental role in the patho-aetiology of rheumatoid arthritis (RA) through its interaction with citrullination and antibody formation [3]. The role of smoking in spondyloarthritis, however, is less clear.

Does it matter? Do we need another reason to tell smokers to stop smoking? Investing in high-quality research on this topic is important for several reasons: First, examining smoking's association with RA led to improved understanding of the disease; if smoking has a role in SpA the same goal may be pursued. Second, SpA patients may be more likely to quit if they know that smoking not only could reduce longevity but also their quality of life, for example, through extra-articular disease manifestations or functional impairment. Lack of awareness about the link between smoking and RA was identified as an important barrier to smoking cessation in RA patients [4]. Third, allocating resources for additional targeted smoking cessation may be cost-effective if it improves response to expensive biologic therapies. Finally, research on this topic is important because, as we will see, there are lessons to be learnt for future observational research. In this review, we focus discussion on two main members of the SpA family: axial SpA (axSpA) and psoriatic arthritis (PsA). Our aim is not to question the known harms of smoking or the need for smoking cessation, but instead to collate existing evidence in SpA to inform clinical practice and highlight research needs. As the reader will see, the story is complex and involves fascinating aspects of epidemiologic research.

How big a problem is smoking in SpA?

In 2018, 15% of UK adults were classified as current smokers [2]. The prevalence is much higher in SpA cohorts: 29% in the international ASAS-COMOSPA study and 24% in the BSR biologics register for AS (BSRBR-AS, which recruits axSpA patients). This does not necessarily implicate a causal role. Two-thirds of AS patients in the UK are managed in primary care; hospital-based research samples are likely taken from those with more severe disease. Young adults – who form the majority of SpA cohorts – also have the highest prevalence of smoking: UK adults aged 25 to 34 were much more likely to smoke than those aged 65 and over (prevalence 19 vs 8%) [2].

Potential mechanisms for smoking to impact on SpA?

Cigarette smoke is a cocktail of thousands of chemical components, each can directly influence the immune system or indirectly through, for example, modifying the oral microbiome [5,6]. The overall effects include increased free radical burden and auto-reactive B cell activity, decreased neutrophil/T-cell activity and decreased cytokine production [6]. Smoking has a dose-response relationship with RA risk, severity and ACPA positivity. Similar associations have been described for other autoimmune disorders such as SLE and Graves' disease [6,7]. Smoking's role in diseases towards the auto-inflammatory end of the spectrum (less female preponderance and autoantibodies, greater implication for mechanical stress, etc [8]) is less clear. Current smokers have lower risk and severity of ulcerative colitis, but the opposite is true in Crohn's disease [6]. In Behçet's disease – a condition patho-mechanistically related to SpA [9] - current smokers have fewer oral aphthae and cessation may aggravate oral disease [10,11].

To make matters more complex, many factors related to smoking may also influence both incidence and severity of SpA; smoking is associated with manual occupations, unemployment, lower physical activity, lower educational attainment, BMI, and other lifestyle and socioeconomic factors [2,12–15]. Untangling the independent impact of smoking from these confounding factors is a major challenge.

Smoking vs incidence and onset of SpA

This and the following sections are supported by systematic literature searches and, where possible, meta-analyses. Detailed methods (search strategy, statistics) and results (flowchart, summary of studies found, forest and funnel plots) are available in online supplementary materials.

Smoking is often said to increase the risk of axSpA. The only study is from the Norwegian population case-control study that reported twice the odds of self-reported AS (n=107) in current compared to never smokers [16]. Although the authors tried to confirm diagnoses where possible, the cohort was atypical: there were fewer males than females (0.7:1). The validity of self-reported diagnosis is uncertain: a high number of self-reported cases (n=174) in the first wave of the study no longer reported AS in the second, and the incidence of AS was much higher than other studies. Past smoking and pack years did not demonstrate a dose-response association with incidence. Lastly, the independent causal role of smoking is uncertain, since many important confounders listed above were unaccounted for.

Smoking has also been associated with earlier onset of inflammatory back pain. In 654 early axSpA patients from the DESIR cohort (63% HLA-B27 positive, 29% meeting modified New York criteria), ever smokers reported symptoms 1.5 years earlier than never smokers (P=0.04) [17]. A similar sized difference was seen for age at onset of peripheral arthritis and enthesitis in this study, although not statistically significant. No information on pack-years was available and analyses were not adjusted for important confounders, except alcohol status. Significant differences in age at symptom onset were not observed in 4 other studies identified through literature search [12,18–20]. The weighted mean difference between ever and never smokers in all 5 studies was 0.1 years (Table 1). Differences between current and non-current smokers was more consistent, but not statistically or clinically significant. An independent role of smoking in axSpA onset is unsupported by consistent evidence and subject to citation bias.

The evidence for psoriatic arthritis (PsA) is more convincing. Compared to never smokers, current smokers had 27%, and past smokers 32%, higher risk of PsA than the UK general population (>6

million people in The Health Improvement Network) [21]. Clearer dose-response associations were shown in >90,000 females from the US Nurses' Health Study II: current (relative risk (RR) 3.1) and past smokers (RR 1.5) had higher risk than never smokers; risk also increased monotonically with pack-year exposure [22]. Both studies adjusted for BMI and alcohol intake, while the latter also accounted for physical activity; neither included socioeconomic status. These findings are consistent with the increased risk of psoriasis among smokers [23]. Interestingly, the relationship between smoking and PsA is reversed when restricted to only those with psoriasis (i.e., smoking appears 'protective' for joint disease) [21,24]; a methodological artefact – collider bias – may explain this and several other paradoxes, as we will discuss later.

Disease mechanisms at the skin, joints, axial skeleton and other sites in SpA are likely to differ, as suggested by differential efficacy of anti-cytokine therapies [25]. The concordant effects of smoking in psoriasis and PsA, but not axSpA, could contribute to improved understanding of their pathology.

Smoking vs disease severity: cross-sectional studies

We identified 18 cross-sectional studies comparing axSpA disease severity according to smoking status and one PsA study [12,17–20,26–38] (Supplementary Table S1). (We use 'disease severity' to encompass disease activity and other outcomes such as function and quality of life.) When comparisons were meta-analyzed, ever-smokers had significantly higher BASDAI, BASFI, spinal pain and poorer quality of life than never smokers (table 1). Effect sizes were larger when comparing current and non-current (i.e., past and never) smokers. In a recent analysis of the BSRBR-AS, these differences remained significant after adjusting for education, deprivation, BMI, comorbidities and alcohol status [12]; smokers in this study also reported worse sleep, fatigue and mental health, but not ESR or CRP. Meta-analysis showed no clinically meaningful or statistically significant difference in ESR according to smoking status. Current smokers had 2mg/dl higher CRP on average than non-current smokers.

Only one PsA study met our inclusion criteria [38]. In 1185 Swedish survey respondents with PsA (59%

responded), ever smokers reported poorer quality of life (0.04 units in EQ-5D), global health, pain and fatigue (by 0.3 to 0.4 units out of 10) than never smokers, but not HAQ [38]. We excluded baseline comparisons from longitudinal studies of biologic-treated cohorts because differences were masked by their already high disease activity [39,40].

There is consistent evidence that SpA severity is associated with smoking. But as with all cross-sectional studies, the direction of causation cannot be determined; for this we turn to longitudinal designs.

Table 1. Summary of meta-analysis results presented as weighted mean difference (95% confidence interval).

	Ever vs never smokers		Current vs non-current smokers	
Age of symptom onset, years	0.07 (-1.01, 1.14)	n=5 I^2=55%	-0.63 (-1.34, 0.07)	n=4 I^2=0%
BASDAI	0.58 (0.35, 0.81)	n=10 I^2=61%	0.91 (0.61, 1.20)	n=9 I^2=70%
BASFI	0.83 (0.20, 1.47)	n=3 I^2=81%	0.81 (0.34, 1.27)	n=8 I^2=87%
Spinal pain	0.69 (0.37, 1.01)	n=4 I^2=56%	0.83 (0.20, 1.47)	n=3 I^2=81%
CRP, mg/dl	1.45 (-0.08, 2.99)	n=8 I^2=65%	1.93 (0.47, 3.38)	n=5 I^2=0%
ESR, mm/hr	0.51 (-1.76, 2.78)	n=8 I^2=65%	1.11 (-1.46, 3.68)	n=6 I^2=54%
ASQoL	n/a	n/a	2.03 (-0.21, 4.26)	n=5 I^2=93%

n=number of studies; I^2, measure of estimate heterogeneity; ASQoL, AS quality of life questionnaire. Estimates were from random-effects models; detailed methodology and forest plots are shown in supplementary materials.

Smoking vs disease severity: longitudinal studies

Six longitudinal studies specifically examined the role of smoking in SpA (5 axSpA, 1 PsA), while 16 included smoking in their study of other exposures or predictors (8 axSpA, 4 SpA, 4 PsA) ([41–62] summarized in Supplementary Table S2). All except 4 examined response to treatment. Results were

too heterogeneous to perform meta-analysis. We focus discussion on studies of treatment response with regard to three outcome types: 1) binary response criteria (reaching a target, e.g., ASDAS<1.3) at a specific time point, 2) continuous change over time (e.g. ΔBASDAI), and 3) risk of treatment discontinuation (time-to-event analysis).

There is consistent evidence that smokers have lower odds of binary response than non-smokers in unadjusted analyses (Supplementary Table S1). Another consistent finding is that statistically significant effects generally became smaller and non-significant after adjusting for confounders. Other smoking-related factors clearly also influence treatment response. Only 5 out of 11 axSpA (0 of 3 PsA) studies reported significant *adjusted* odds ratios. Current smokers with AS had 47% lower odds of BASDAI50/2 (50% or 2-unit reduction) in the DANBIO registry [58]. In a UK axSpA cohort, current smokers had 65% lower odds of achieving BASDAI<3 at 6 months than never smokers [45]. In an early SpA cohort (DESIR; 68% ASAS criteria), current smokers had 66% lower odds of ASDAS inactive disease (<1.3) at 2 years [51]. Current smokers had 95% lower odds of ASDAS inactive disease at 3 years when restricting the DESIR cohort to peripheral SpA (ASAS criteria) [52]. Using the Swiss Clinical Quality Management Cohort (SCQM), Ciurea et al reported current smokers with axSpA to have 46% lower odds of BASDAI50 at 1 year [57].

In contrast to the large effect sizes above, all studies (4 axSpA, 0 PsA) using change in continuous outcomes found no clinically or statistically significant differences according to smoking status [41,57,59,60]; that is, although smokers had more severe disease at TNFi initiation than non-smokers, they experience the same absolute reduction in disease outcomes over time. In the same SCQM study by Ciurea et al, difference in BASDAI change over time (ΔBASDAI) was not clinically or statistically significant, despite current smokers having less than half the odds of BASDAI50 [57]; a similar contrast was observed by Lord et al for ever/never smokers [41]. Ciurea et al did find statistically significant differences between current and never smokers in the subgroup with elevated baseline CRP (by 0.75 units in BASDAI and 0.69 units in ASDAS) [57]. This stratification is difficult to interpret since 1) policy makers are unlikely to implement targeted smoking cessation only in patients with elevated CRP, and 2) both axSpA disease activity and smoking are causes of elevated

CRP. The latter has potential to generate spurious findings, as suggested by ΔBASDAI between ever vs never smokers being twice as large as current vs never smokers, among the remaining patients with normal baseline CRP (i.e., opposite of biologic gradient and results for the subgroup with elevated CRP).

Discrepancies between continuous and binary responses may be due to methodological differences [60]. Since smokers have more severe disease at baseline, fewer of them would meet a binary definition of response even if improvement were identical across all patients: if all patient improved by 3 BASDAI units in the BSRBR-AS, 40% of never smokers would achieve BASDAI50 response compared to 28% current smokers [60]. All individuals with high starting disease activity (whether they are smokers or grouped according to any other exposure) will be less likely to reach remission (or similar binary response definition), since they need to achieve a greater absolute improvement.

What about treatment discontinuation? Current smoking (vs non-current) was not associated with TNFi discontinuation (HR_{adj} 0.92; 95%CI 0.66 to 1.28) in another SCQM study focusing on BMI in axSpA [47]. Three other axSpA studies also did not demonstrate an effect of smoking on treatment discontinuation [48,49,61]. In the DANBIO register, however, current smokers with axSpA (HR_{adj} 1.41 [58]) and PsA (HR_{adj} 1.20 [58]) had higher risk of TNFi discontinuation than non-smokers, but they did not account for relevant confounders. This study (like many others) did not adjust for baseline differences in disease activity on the premise that they were 'intermediate variables' (i.e., smoking → high baseline disease activity → treatment response); adjusting for mediators would indeed be inappropriate. However, this approach relies on the assumption that smoking causes high baseline disease activity, and not the converse. It is possible that patients smoking behavior is influenced by their symptoms.

In a qualitative study of barriers to smoking cessation, Aimer et al found that many RA patients 1) used a smoking to distract from or help with pain; 2) were unable to move/exercise so they smoked instead; 3) used smoking as a coping mechanism [4]. Could disease activity drive smoking behavior more so than the converse? Here are some insightful quotes from their paper [4]: "You know

smoking honestly does seem the only thing I can do"; "It's something to do with your hands when you don't feel like doing anything." These insights may explain why cross-sectional associations were not replicated in longitudinal studies. They also highlight the need to test assumptions often invoked in longitudinal analyses.

When a smoker with axSpA is started on treatment, it is fair to assume that s/he will be less likely to achieve many binary definitions of response. But is this caused by smoking or confounding factors? The *independent* association between smoking and response is likely small or absent when relevant confounders are considered. The same patient in a parallel universe - with the same socioeconomic status, lifestyle, baseline disease severity etc – but who does not smoke, will be equally unlikely to respond. There is currently insufficient evidence to support targeted smoking cessation with the primary aim of improving the cost-effectiveness of biologic treatment. That is not to take away from the importance of smoking cessation. Smokers have worse disease before starting on treatment; therefore smoking may contribute to disease evolution up to that point. Cessation may help reduce functional decline; longitudinal change in HAQ was poorer in smokers with axSpA [43] and PsA [53]. Boonen et al found higher absenteeism in current smokers over 2 years (although not withdrawal from work or presenteeism) [44]. Randomised controlled trials are needed. To date, only 2 trials have been completed for smoking cessation in inflammatory arthritis (both in RA), neither measured disease activity [63].

Smoking vs radiographic progression

Disease modification in inflammatory arthritis is underpinned by reduction in radiographic progression. One PsA and 17 axSpA studies of radiographic progression were found through literature search ([14,64–80] summarized in Supplementary Table S3). Most axSpA studies examined spinal progression, as change in mSASSS (modified Stoke AS Spinal Score) and new syndesmophyte formation. Results were unsuitable for meta-analysis. Only 3 of the 14 studies reported significant associations between smoking and radiographic progression. The most commonly cited is the 2012 paper by Poddubnyy et al [68], where current smoking (along with baseline damage and elevated

CRP) predicted radiographic progression (increase of ≥2 mSASSS units over 2 years) in 210 mostly non-TNFi treated axSpA patients. Current smokers had over twice the odds of progression than non-current smokers in 4 models (OR_{adj} 2.3 to 2.5; P=0.04 to 0.06) that also included classification (AS vs nr-axSpA), presence of syndesmophytes, sex and each of 4 representations of ESR/CRP. Using similar exposure/outcome definitions, Kim et al reported 3-times higher odds of progression in axSpA patients <50 years old, but these large effect sizes were not replicated in studies led by Min (OR_{adj} 1.04; 95%CI 0.57, 1.91), Braun (OR_{adj} 0.97; 95%CI 0.54, 1.76) or Joo (OR_{adj} 1.48; 95%CI 0.67, 3.27) [66,73,79]. Deminger et al also failed to find a significant effect over 5 years [76]; male ever smokers in this study had over 3 times the odds of progression, but effect sizes were reversed in females (i.e., smokers had lower odds of progression). Only 1 of the 3 studies examining pack year exposure found a significant association with ΔmSASSS [78]. None of the 4 studies of new syndesmophyte formation found statistically significant associations with smoking, although effect sizes were large in both directions (OR_{adj} ranged from 0.64 to 2.43) [66,68,75,79].

None of the above studies can tell us whether smoking is an independent predictor of radiographic progression (above the confounding effects of occupation, physical activity or other lifestyle/socioeconomic factors). Using a detailed dataset, Ramiro et al found that axSpA patients with physically demanding jobs had greater radiographic progression (2.2 vs 1.8 mSASSS units/2 years) than those with less physical jobs [14]. The equivalent analysis for smoking was not significant (P=0.22). They also found that job type was numerically associated with mSASSS among smokers (progression 1.5 vs 1.2 mSASSS units/2 years). Taken together, these findings suggest that occupation, rather than smoking, may be a more important causal candidate for radiographic progression. The sole study of radiographic progression in PsA found no association between ever smoking and scoring of progression in 42 joints; the authors did, however, find associations with high levels of occupation-related mechanical stress [80]. This is a more biologically plausible hypothesis, since mechanical stress is key to SpA pathophysiology [81].

What about radiographic progression at the sacroiliac joint? Three studies were found through systematic searches. Using the same cohort as above, Poddubnyy et al did not find an association

between smoking and SIJ progression [69]. Dougados et al reported 3.3 fold higher odds (95%CI 1.0, 11.5) of progressing from non-radiographic axSpA to AS after 2 years [65] – an effect that became attenuated and non-significant after 5 years (OR_{adj} 1.40 for HLA-B27 positive, OR_{adj} 0.97 for negative) [64]. Measurement error is problematic for sacroiliac joint grading and may mask any real effects.

In summary, the role of smoking in radiographic progression in SpA is far from clear. Citation bias for positive associations may impede further, improved analysis of this interesting relationship. Future studies would benefit from examining confounding factors associated with mechanical stress in parallel.

Smoking vs EAMs

AxSpA is associated with increased risk of psoriasis (50% higher than age- and sex-matched controls), uveitis (16-fold higher) and IBD (3-fold higher) [82]. Only a few studies examined the association between smoking and EAMs. In a cross-sectional analysis of the BSRBR-AS, current (but not past) smokers had 48% increased risk of psoriasis [12], which is consistent with increased risk of psoriasis among smokers in the general population [23]. This risk should be emphasised to smokers since psoriasis has significant impact on body image, quality of life and mental health [83].

The BSRBR-AS study also found current smokers to have 26% *lower* risk of uveitis compared to ex- or never smokers [12]. This is immediately counterintuitive since smoking is a risk for uveitis in the general population [84] and resembles the case discussed earlier: smoking increases the risk of PsA in the general population, but appears 'protective' of PsA among people with psoriasis. The PsA paradox has been solved using population level data [21] and is said to be a consequence of the analysis (conditioning on an intermediate, potentially collider, variable). Equivalent analyses remain outstanding for axSpA. (Note that smoking needs to be causally associated with axSpA - like it is with psoriasis - for this explanation to be used analogously.) It is not impossible for smoking to have a protective role, as is the case in ulcerative colitis and Behcet's disease – both related to uveitis and SpA [85]. If smoking has a genuine protective effect for uveitis, then it should also protect against

recurrent attacks. This was not the case: among those with uveitis, the authors of the BSRBR-AS study found 33% increased risk of recurrent attacks in current vs never smokers; 76% increased risk in current vs never smokers on biologics [86]. Further delving into such subsamples runs the risk of introducing more bias, thus analyses using population level data are needed.

In the BSRBR-AS analysis, ex-smokers (but not current smokers) also had non-significantly elevated risk of IBD (RR 1.34), although there was insufficient power to interrogate Crohn's and ulcerative colitis separately [12]. Adding to the catalogue of paradoxes, the authors reported a small and non-significant reduced risk for peripheral arthritis (RR 0.89). This was supported by findings from the French DESIR cohort, where peripheral arthritis was significantly associated with non-smoking (OR 1.58; 95%CI 1.10 to 2.27) [87]. These findings are inconsistent with what we know about smoking being associated with increased risk of peripheral psoriasis-related arthritis.

There are fewer studies in PsA. Like axSpA, PsA is also associated with higher risk of uveitis (RR 3.6) and Crohn's disease (RR 3.0) than the general UK population [88]. This study found that current smokers had higher incidence of Crohn's disease than non-current smokers (effect size unreported). More PsA studies are needed.

How do we interpret these results?

We highlighted several counterintuitive findings, such as smoking appearing protective of uveitis and peripheral arthritis. Smoking also appeared protective of disease and radiographic progression in some studies. Contradictions like these are not new in other areas of observational research: it is well-known that infants born to smokers have lower birth weight and higher mortality compared to non-smokers, yet maternal smoking appeared *beneficial* for infant mortality among infants with low birth weight [89]. Such paradoxical associations can emerge through inappropriate analyses (Figure 1), even in the absence of any effect from smoking. Other potential instances where collider bias may explain paradoxes in the rheumatology literature are reviewed in reference [90]. Although tempting to summon collider bias for every counterintuitive finding, we concede that it may not be

the only explanation [60]; this bias does, however, highlight the need for better designed observational research in population studies. Recommendations to reduce bias and improve design are beyond the scope of this review but can be found in references [21,90,92].

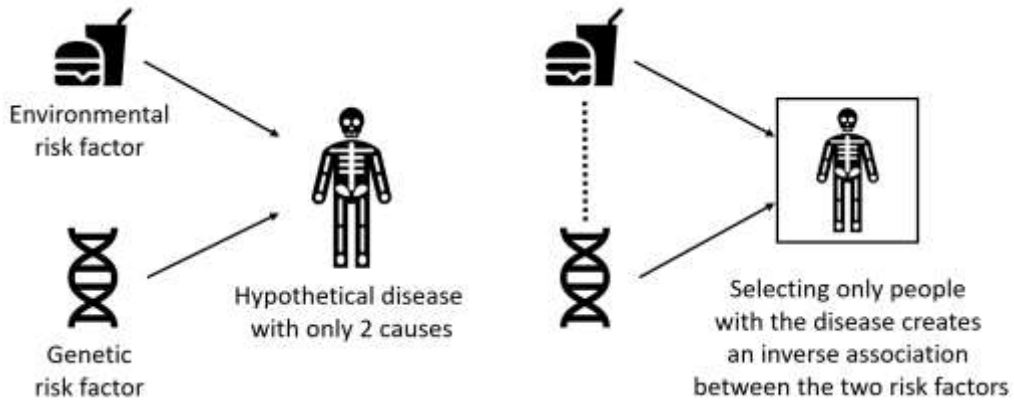

Figure 1. Collider bias. Imagine there is a disease that has only two causes: an environmental factor and a genetic factor. Imagine also that these two factors are completely unrelated in the general population (left panel). If we only study patients with this disease, an artefactual association will emerge between the two factors (right panel). If a patient does not have the gene, then the environmental factor must have caused the disease. Conversely, if a patient has never been exposed to the environmental factor, then it must have been the genetic factor that caused the disease. An inverse relationship is thus observed by conditioning on (or selecting, stratifying, "adjusting" using) a variable that has two common causes, i.e., a 'collider'. We recommend reference [93] for a comprehensive introduction to these topics.

We often talk about smoking as a '*modifiable* risk factor' in the same breath as calling it a 'predictor.' The former calls for examination of its potential *causal* role and is distinct from the latter [94]; even great predictors may not necessarily be a cause. Recall that Sir Bradford Hill recommended criteria in addition to strength of association, among which are: consistency, biological gradient (i.e., dose-response) and specificity (i.e., not due to another factor). None of these are confirmed by

existing axSpA evidence. We reiterate smoking's association with manual occupations, BMI, lower educational attainment, and other lifestyle and socioeconomic factors [2,12–15], which are seldom adequately considered. Causation is also supported by temporality (i.e, cause before effect): Insights from Aimer and colleagues' qualitative study in RA highlight the possibility that disease activity influences smoking behaviour. Reverse causation is not implausible: alcohol was observed to 'improve' symptoms of rheumatic disease [13,95], but evidence is emerging that it is instead high symptom severity that leads to reduced alcohol intake [96].

Conclusion

Smoking is a major cause of morbidity and mortality worldwide. It is associated with increased risk of psoriasis in axSpA and possibly also uveitis flares and IBD. EAMs, particularly when severe, can significantly impact quality of life and many other outcomes; therefore, risks should be highlighted to patients who continue to smoke. Smoking also increases risk of psoriatic arthritis. More studies are needed to examine the effect of smoking on longitudinal PsA outcomes and EAMs. Further research is also needed on whether counterintuitive associations between smoking and uveitis/arthritis arose from biological or methodological phenomena. Regardless of inconsistencies in existing evidence, we should support patients and encourage smoking cessation at every opportunity due to the many well-established harms.

Acknowledgements

We thank Prof Gary Macfarlane, Dr Gareth Jones and the staff of the BSRBR-AS register for their contributions to previous smoking studies, on which much of the discussion was based.

Funding: none

Disclosures: The authors declare no conflicts of interest.

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